

Exhibit 17

Exhibit 17**U.S. Patent No. 6,258,540: Anticipation**

Claim 1	Anticipation Analysis
<p>1. A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises</p>	<p>The Kazakov paper and its methods involved the use of maternal serum and the amplification of cell-free nucleic acid sequences which would have unavoidably amplified paternally inherited fetal sequences. These amplified sequences were then detected and analyzed by gel electrophoresis, which involves passing an electric current through a gel containing the nucleic acid sample to separate the nucleic acids by size. While the methods used by Kazakov and his colleagues were not able to distinguish which sequences were paternally inherited, if, as Sequenom contends, the '540 patent is so broad that it does not require such, then the methods described in the Kazakov et al. paper would be covered by the claims of the '540 patent.</p> <p>Kazakov and his colleagues prepared serum samples from men, non-pregnant women, and women in their first and third trimesters of pregnancy, including women with a disorder of pregnancy known as preeclampsia, using standard approaches. (Ex. 4 at p. 233.) Cell-free DNA was isolated from the serum samples, <i>i.e.</i>, all proteins were removed to leave only DNA, by conventional procedures. (<i>Id.</i>) DNA is usually isolated before analysis because proteins are known to interfere with DNA analysis.</p>
<p>amplifying a paternally inherited nucleic acid from the serum or plasma sample and</p>	<p>This cell-free DNA was subjected to DNA amplification using PCR, a technique I described earlier. (<i>Id.</i>) The particular sequences that were amplified are known as “Alu repeats.” (<i>Id.</i>) These are repetitive DNA sequences that occur over a million times in the human genome (Batzer & Deininger Nat Rev Genet 2002, Ex. 14). They are called “Alu repeats” because they can be recognized and cut by an enzyme called Alu I. Over 10% of human DNA consists of Alu repeats. Alu repeats are widely scattered throughout the genome and are present on all human autosomes (<i>i.e.</i>, chromosomes 1-22) as well as both the X and Y chromosomes. Thus, Alu repeats are present on every chromosome in the fetal genome, both those that are paternally inherited and those that are maternally inherited. They occur on the fetal Y chromosome, if the fetus possesses one, as well as all non-Y fetal chromosomes. By</p>

	<p>amplifying Alu repeats of cell-free DNA in the serum of pregnant women, which contains cell-free fetal DNA, Kazakov and his colleagues necessarily amplified fetal nucleic acid from a paternally inherited nucleic acid.</p> <p>Three different primers—the short DNA sequences necessary to start each round of the PCR amplification process, and that target specific regions of DNA—called B1, C2, and Tc65 were used to target the Alu repeats. (Ex. 4 at p. 233.) I compared the DNA sequences of these three primers to the Alu repeat sequences, as shown in Exhibit 15, and confirmed that they would have led to the amplification of Alu repeats on every human autosome as well as both the X and Y chromosomes (Batzer & Deininger Nat Rev Genet 2002; Grover et al. Bioinformatics 2002; Ellis et al. Nature 1989; Daniels et al. Nucl Acids Res 1983).</p>
detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.	Kazakov and his colleagues then detected these amplified Alu repeats, including the paternally inherited Alu repeats of fetal origin, using gel electrophoresis. (Ex. 4 at p. 233.)
Claim 2	Anticipation Analysis
2. The method according to claim 1, wherein the foetal nucleic acid is amplified by the polymerase chain reaction.	Claim 2 of the '540 patent is met by Kazakov et al. (Tsitologiia 1995), as the authors did in fact use PCR to amplify the fetal nucleic acid present in maternal serum. (Ex. 4 at p. 233.)
Claim 8	Anticipation Analysis
8. The method according to claim 1, wherein the presence of a foetal nucleic acid from a paternally-inherited non-Y chromosome is detected.	Claim 8 is also met by Kazakov et al. (Tsitologiia 1995) as the claims are interpreted by Sequenom. As explained earlier, by amplifying and detecting Alu repeats of cell-free DNA in the serum of pregnant women (Ex. 4 at p. 233), which contains cell-free fetal DNA, Kazakov and his colleagues necessarily detected fetal nucleic acid from a paternally inherited non-Y chromosome.
Claim 19	Anticipation Analysis
19. The method according to claim 1, wherein the sample contains foetal DNA at a fractional concentration of total DNA of at least about 0.14%, without subjecting it	The serum samples containing cell-free fetal DNA used by Kazakov et al. (Tsitologiia 1995) would have had at least the fractional concentration of fetal DNA to total DNA specified in claim 19. Kazakov and his colleagues performed their study on serum from pregnant women in the first and third trimesters of pregnancy, including pregnant

to a foetal DNA enrichment step.	women suffering from preeclampsia. (Ex. 4 at p. 233.) It is well established that the physiology of normal pregnant human females gives rise to a fractional concentration of cell-free fetal DNA to total DNA in serum or plasma far in excess of 0.14%, at least from late in the first trimester onwards (Lun et al. Clin Chem 2008; Lo Clin Chem Lab Med 2012; Lo et al. Am J Hum Genet 1998). Furthermore, as Kazakov and his colleagues demonstrated, the fractional cell-free fetal DNA concentration to total DNA in the serum of pregnant women suffering from preeclampsia is higher than in normal pregnancies. Thus, the fractional concentration of cell-free fetal DNA to total DNA in the serum or plasma of pregnant women with preeclampsia also much exceeds 0.14%.
Claim 20	Anticipation Analysis
20. The method according to claim 19, wherein the fractional concentration of foetal DNA is at least about 0.39%.	The serum samples containing cell-free fetal DNA used by Kazakov et al. (Tsitologiia 1995) would have had at least the fractional concentration of fetal DNA to total DNA specified in claim 20. Kazakov and his colleagues performed their study on serum from pregnant women in the first and third trimesters of pregnancy, including pregnant women suffering from preeclampsia. (Ex. 4 at p. 233.) It is well established that the physiology of normal pregnant human females gives rise to a fractional concentration of cell-free fetal DNA to total DNA in serum or plasma far in excess of 0.39%, at least from late in the first trimester onwards (Lun et al. Clin Chem 2008; Lo Clin Chem Lab Med 2012; Lo et al. Am J Hum Genet 1998). Furthermore, as Kazakov and his colleagues demonstrated, the fractional cell-free fetal DNA concentration to total DNA in the serum of pregnant women suffering from preeclampsia is higher than in normal pregnancies. Thus, the fractional concentration of cell-free fetal DNA to total DNA in the serum or plasma of pregnant women with preeclampsia also much exceeds 0.39%.
Claim 21	Anticipation Analysis
21. A method of performing a prenatal diagnosis, which method comprises the steps of:	Prenatal diagnosis as defined in the '540 patent "covers determination of any maternal or foetal condition or characteristic which is related to either the foetal DNA itself or the quantity or quality of the foetal DNA in the maternal serum or plasma," including "detection and monitoring of pregnancy-associated conditions such as pre-eclampsia." (Ex. 2 at 2:6-14.) Kazakov and his colleagues were able to provide a diagnosis of preeclampsia based on the increased

	quantity of cell-free fetal nucleic acid in maternal serum. (Ex. 4 at p. 233.)
(i) providing a maternal blood sample;	Kazakov and his colleagues obtained blood samples from pregnant females. (<i>Id.</i>)
(ii) separating the sample into a cellular and a non-cellular fraction;	As explained previously, a “cellular” fraction means a portion of the sample that contains cells. A “non-cellular” fraction means a portion of the sample that does not contain cells. Kazakov and his colleagues separated each maternal blood sample into cellular and acellular fractions, the acellular fraction in this case being serum. (<i>Id.</i>)
(iii) detecting the presence of a nucleic acid of foetal origin in the non-cellular fraction according to the method of claim 1;	As I described in my analysis of claim 1, Kazakov and his colleagues detected the presence of nucleic acid of fetal origin in the non-cellular fraction using gel electrophoresis. (<i>Id.</i>)
(iv) providing a diagnosis based on the presence and/or quantity and/or sequence of the foetal nucleic acid.	Kazakov and his colleagues also made a diagnosis of preeclampsia based upon the increase in cell-free DNA, postulating that the increase came from the fetus. (<i>Id.</i>)
Claim 22	Anticipation Analysis
22. The method according to claim 21, wherein the non-cellular fraction as used in step (iii) is a plasma fraction.	Though serum was used by Kazakov and his colleagues, I interpret the Kazakov paper as suggesting that either maternal plasma or serum can be used as a source of the cell-free DNA. Specifically, the authors explain that “[t]he use of serum instead of plasma for the analysis of the DNA of the blood can be justified if one observes the conditions for formation of a thrombus at room temperature and immediate removal of the serum from the thrombus (Leon et al., 1977; Shapiro et al., 1983). Such was done in the present investigation.” (Ex. 4 at p. 233.) Kazakov and his colleagues thus explain their rationale for using serum, and indicate that plasma would be a suitable alternative.
Claim 24	Anticipation Analysis
24. A method for detecting a paternally inherited nucleic acid on a maternal blood sample, which method comprises:	As I already discussed in my analysis of claim 1, Kazakov and his colleagues detected paternally inherited nucleic acid on a maternal blood sample by preparing serum samples from the blood of pregnant females and amplifying and detecting cell-free nucleic acids in these samples.
removing all or substantially	Nucleated cells are cells that contain a nucleus. Most

all nucleated and anucleated cell populations from the blood sample,	human cells are nucleated. Anucleated cells are cells that do not contain a nucleus. Some cell types normally lack a nucleus, such as normal adult red blood cells, whereas others lack a nucleus as a result faulty cell division. Serum, which is the sample on which Kazakov and his colleagues performed their experiment (Ex. 4 at p. 233), does not contain nucleated or anucleated cells. Kazakov and his colleagues prepared serum samples from maternal blood samples. (<i>Id.</i>)
amplifying a paternally inherited nucleic acid from the remaining fluid and subjecting the amplified nucleic acid to a test for the Paternally inherited fetal nucleic acid.	As I already discussed in my analysis of claim 1, Kazakov and his colleagues amplified and detected paternally inherited nucleic acid in the serum when this claim is interpreted as broadly as Sequenom proposes. While this claim refers to “subjecting the amplified nucleic acid to a test for the [p]aternally inherited fetal nucleic acid,” there is nothing in the patent specification that suggests that this is any different than “detecting a paternally inherited nucleic acid” as appears earlier in the claim and in claim 1.
Claim 25	Anticipation Analysis
25. A method for performing a prenatal diagnosis on a maternal blood sample, which method comprises	Prenatal diagnosis as defined in the '540 patent “covers determination of any maternal or foetal condition or characteristic which is related to either the foetal DNA itself or the quantity or quality of the foetal DNA in the maternal serum or plasma,” including “detection and monitoring of pregnancy-associated conditions such as pre-eclampsia.” (Ex. 2 at 2:6-14.) Kazakov and his colleagues were able to provide a diagnosis of preeclampsia based on the increased quantity of cell-free fetal nucleic acid in maternal serum. (Ex. 4 at p. 233.)
obtaining a non-cellular fraction of the blood sample	A non-cellular fraction of a blood sample is a portion of the sample that does not contain cells. Serum, which was used in the experiment of Kazakov and his colleagues (<i>id.</i>), is a non-cellular fraction of a blood sample.
amplifying a paternally inherited nucleic acid from the non-cellular fraction	As I already discussed in my analysis of claim 1, Kazakov and his colleagues amplified paternally inherited nucleic acid in the serum when this claim is interpreted as broadly as Sequenom proposes.
and performing nucleic acid analysis on the amplified nucleic acid to detect paternally inherited fetal	As I already discussed in my analysis of claim 1, Kazakov and his colleagues detected paternally inherited nucleic acid in the serum when this claim is interpreted as broadly as Sequenom proposes. While this claim refers to “performing nucleic acid analysis . . . to detect paternally inherited fetal

nucleic acid.	nucleic acid,” there is nothing in the patent specification that suggests that this is any different than the “detecting” step in claim 1.
---------------	--